IN THE

Supreme Court of the United States

OCTOBER TERM, 1979

No. 79-136

SIDNEY A. DIAMOND, COMMISSIONER OF PATENTS AND TRADEMARKS, *Petitioner*,

v.

ANANDA M. CHAKRABARTY, *Respondent.*

BRIEF OF DR. GEORGE PIECZENIK AS AMICUS CURIAE

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I. INTEREST OF THE AMICUS

Dr. George Pieczenik, appearing herein as *amicus curiae,* is a molecular biologist and computer scientist on the faculty of Rutgers University. Dr. Pieczenik received his undergraduate training at Harvard University, obtained a masters degree in radiation physics from the University of Miami, and a doctor of philosophy degree from New York University. His doctoral dissertation was entitled "Genetic Code Constraints on Amino Acid and Nucleotide Sequences," in which he investigated the genetic code of living organisms from the standpoint of a language having internal

constraints and internally consistent syntax. These studies, in combination with subsequent work carried out at Rockefeller University and the M.R.C. Laboratory of Molecular Biology, Cambridge, England, have consequences in molecular biology which received national press coverage (*Time*, April 4, 1977, p. 47). Dr. Pieczenik has been one of the pioneer scientists in the development of techniques for determining nucleotide sequences of DNA and RNA, and has developed techniques for the construction of transfer vectors in recombinant DNA technology which are the subject of a pending patent application. A list of his scientific publications is attached hereto as an Appendix. Dr. Pieczenik has no financial interest in or connection with Respondent.

Dr. Pieczenik has been active in public affairs relating to science and technology in his area of expertise. In this regard, he has testified before the Committee on Science and Technology of the House of Representatives on matters relating to the safety of recombinant DNA research.

Dr. Pieczenik is concerned that the decision in the instant case be made along lines that are rational and meaningful in terms which he and other researchers similarly situated can comprehend as guidelines for what may or may not be patented in this area of technology. He is further concerned that the Court should have the benefit of direct input from research workers in this art with respect to the nature of the inventions likely to be affected by its holding and the consequences thereof as applied to the existing patent statute.

II. STATEMENT AND ARGUMENT

The Petitioner requests reversal of the decision below *on the ground that the subject matter is a living organism.* Whatever this Court's holding, its decision will necessarily distinguish between patentable and unpatentable subject matter in the area of biotechnology. It is essential that this line be drawn on the basis of the known scientific realities as applied to the existing law. This Court is not constrained to accept the conceptual framework suggested by the Petitioner.

The distinction between living and non-living matter has no real meaning in relation to this technology. That which is living is typically described in terms of a set of attributes[1] which, when all present, are considered indicia of life. There is no single fundamental property, law of nature, or operating principle, which distinguishes that matter which we call living from that which we do not.[2] To attempt to separate

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[1] See, for example, Luria, S. E. and Darnell, James D., Jr., *General Virology,* 2nd Edition, John Wiley & Sons, Inc., New York, 1967, pp. 5-8. Commonly mentioned attributes include cellular organization, ability to derive energy from sources in the environment, motility, responsiveness to change in environmental conditions, capacity to replicate, and so forth.

[2] The notion of vitalism holds that, in the last analysis, the phenomena of life can be explained only by the existence of a mysterious "vital force" which operates only within the realm of living matter. Gunther Stent, in his text *Molecular Genetics,* (W. H. Freeman & Co., San Francisco, 1971, p. 28), notes that a sophisticated version of vitalism may have inspired the interest which many physicists took in biological phenomena following World War II:

> Inspired by the romantic notion of finding "other laws of physics" through the study of genetics, a number of physical scientists left the occupation for which they had been trained

patentable and unpatentable subject matter on the basis of such a concept is to invite confusion in the art, to ignore existing law and to ignore scientific reality.[3]

Amicus therefore invites the Court to consider how the line can best be drawn, irrespective of its ultimate holding, for it is this aspect of the case which will determine whether the decision offers meaningful precedential value for researchers, the Patent and Trademark Office and for the Court of Customs and Patent Appeals, or whether it invites confusion, uncertainty and continued litigation. A definitive decision, ***based on practical reality,*** is urgently needed for future technological advances in this art.

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and addressed themselves to the problem of the nature of the gene. The entry of these new men into genetics and cognate fields in the 1940s produced a revolution in biology that, when the dust had cleared, left molecular biology as its legacy. As part of this revolution, molecular genetics was to develop out of classical genetics, and by the time of the Mendel Centennial in 1965 the nature of the gene was understood. Alas, the physicists were to be cheated out of their reward: no "other laws of physics" had turned up along the way. Instead, as the facts to be set forth in this book will show, the making and breaking of hydrogen bonds seem to be all there is to understanding the workings of the hereditary substance.

[3] The situation presented in the instant case is to be distinguished from those relating to defining the point at which a human being is legally dead. In such cases, the courts are primarily concerned with matters of social justice involving the point at which the constellation of laws relating to the rights and privileges of a living, sentient individual are to be terminated in favor of the operation of those laws relating to a deceased. In contrast, the instant case relates to the development of biotechnology where the law is concerned only with adjudicating intellectual property rights arising out of new discoveries. Legal decisions in this subject area ought not to be based upon a distinction that has no practical significance in the affected subject area.

Between that which is unquestionably living matter and that which is not, there are a great many useful substances of varying chemical complexity.[4] In common they are characterized as possessing some of the attributes of living organisms, but they clearly do not possess them all. The viruses for example are typically composed of nucleic acid (DNA or RNA) and proteins [5] in defined amounts and structural relationships.[6] In pure form [7] viruses exhibit no attributes of living organisms, are unable to grow, multiply or derive

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[4] A partial list would include such obligate parasites as the *Chlamydia* and *Bdellovibrio bacteriovirus* which depend upon some organizational aspect of a living cell for growth and reproduction, the viruses, plasmids (which are composed of DNA) and cloned genes.

[5] See Luria, S.E. and Darnell, J. D., *supra*, p. 2. The terms DNA, RNA and protein are generic names for polymeric chemical substances. DNA is built up from four monomeric building blocks, termed deoxynucleotides, linked in specific sequential array. It is the sequence of the monomers which chemically distinguishes one DNA from another. RNA is structured similar to DNA except that the monomers are ribonucleotides. The monomeric building blocks of proteins are amino acids, primarily selected from a set of twenty amino acids. Individual proteins are chemically distinguished by the exact sequence of amino acids.

[6] Typically, the nucleic acid is contained in a core which is surrounded by a coat of protein components. The viruses vary widely in complexity, the simplest having protein coats composed of repeating subunits of a particular protein forming a precise geometric arrangement. The more complicated viruses may include additionally an envelope containing lipid material derived from the membrane of an infected cell. Some of the simpler viruses, for example, bacteriophage ϕX-174, have been completely characterized chemically, both as to the amino acid sequence of the proteins of the virus and the nucleotide sequence of their nucleic acid component.

[7] Many viruses have geometrically regular shapes and may be purified in crystalline form.

energy from the environment. When combined with susceptible organisma, a virus can cause the replication and assembly of multiple virus progeny, alter the functional characteristics and even the appearance of the organism and, in some cases can induce permanent genetic alteration of the organism.

Certain kinds of DNA molecules also have a dualistic property of being definable like ordinary inanimate chemical compounds, yet being capable of transforming susceptible host cells, altering their functional properties and inducing permanent genetic changes passed on to progeny cells.[8] DNA is, in fact, the chemical substance which embodies the genetic information

[8] Avery, O. T., McCleod, C. M., and McCarty, M., *J. Expt. Med. 79*, 137 (1944), first demonstrated that DNA added to a culture of microorganisms was capable of causing a specific, definable genetic alteration. Despite the fact that DNA molecules are very high molecular weight polymers, most living cells are capable of taking up DNA from the culture medium from which they are grown. Of particular interest in this regard are those DNA molecules termed plasmids. Plasmids are DNA molecules having the ends joined to form a closed loop and contain the necessary genetic determinants for their autonomous replication, once inserted into a living cell. They may, and typically do, contain additional genetic determinants, for example, for resistance to an antibiotic. A bacterial cell may harbor one or more plasmids which replicate autonomously within the cell and are distributed to daughter cells when the cell divides. Novel plasmids containing genes from heterologous sources can be constructed by recombinant DNA techniques or by more conventional microbial genetics techniques. Chakrabarty's organism was derived by a multistep process by which several distinct plasmids bearing various selected genetic determinants were introduced, conferring upon the organism bearing them the ability to metabolize various sorts of hydrocarbons. Selection was "phenotypic," that is, based upon functional properties of the plasmid-bearing organism in defined environments.

of all living organisms.[9] Its chemical nature is well known and can be found in present day high school biology texts.[10]

The essential feature of the chemical structure of concern here is the exact sequence of deoxynucleotide monomers which constitutes a given DNA molecule.[11] Deoxynucleotide sequences of specific DNA molecules are now ascertainable as a routine matter with a high degree of accuracy.[12] Furthermore, functional DNA

[9] The deoxynucleotide sequence of DNA constitutes a code which specifies the amino acid sequences of all proteins made by the organism. RNA, on the other hand, serves a variety of functions intermediate in the process of translating the genetic code into protein. In some instances, RNA also serves as repository of genetic information. In particular, the genetic material of some viruses is RNA rather than DNA.

[10] See, e.g., Otto, J., and Towle, A., ***Modern Biology***, Holt, Rinehart and Winston, N.Y. (1977) *and* Biological Sciences Curriculum Study, ***Biological Sciences, an Inquiry into Life***, 4th ed. (1980).

[11] A given DNA molecule has a completely definable deoxynucleotide sequence from beginning to end, despite having a molecular weight which may be upwards of hundreds of millions. The number of possible sequences of X monomers is precisely 4^X. In contrast, many patented chemical polymers are only describable in terms of an approximate molecular weight range and have a random arrangement of subunits describable only in terms of their relative proportions. Recently, the complete deoxynucleotide sequence of hepatitis virus DNA was determined. The molecule has 3182 deoxynucleotide subunits and exists in the form of an endless loop. Galibert, F., *et al.*, *Nature 281*, 646 (1979).

A set of endless loop DNA molecules having the same deoxynucleotide sequence could be cut once, at a single site randomly distributed, to yield a population of linear molecules having the same sequence circularly permuted. Such a population is nevertheless uniquely describable in terms of a single sequence, simply by writing the sequence in a circle.

[12] Sanger, F., *et al.*, *Proc. Nat. Acad. Sci. USA 74*, 5463 (1977); Maxam, A. M. and Gilbert, W., *Proc. Nat. Acad. Sci. USA* 74, 560

can be chemically synthesized.[13] Therefore, DNA molecules, as definable and enumerable pure chemical compounds, fall squarely within the ambit of patentable subject matter under 35 U.S.C. § 101.[14]

Further, it is precisely the deoxynucleotide sequence of DNA which accounts for its dualistic nature. The sequence constitutes information to which a living cell is responsive, analogously as an engine to its camshaft or an architect to his blueprints. A DNA molecule introduced into a cell can, in effect, direct the cell to make a protein, according to information encoded in the specific deoxynucleotide sequence of the introduced DNA, and thereby to perform a new function. Furthermore, the introduced DNA molecule can be duplicated manyfold and passed on to progeny cells. The introduced DNA molecule can be reextracted from the cells, many times amplified in amount. For example, bacteria normally sensitive to penicillin can be rendered resistant by introducing into the bacterial cell a DNA molecule which instructs the recipient cell to produce an enzyme that catalytically degrades penicillin. The recipient cell can duplicate the introduced DNA and pass it to progeny cells, so that a new cell strain is

(1977). As a practical matter, the determination of deoxynucleotide sequence of DNA is easier than the determination of amino acid sequence of proteins. It is therefore entirely feasible to deduce the nature of the proteins of an organism from analysis of its DNA. See Galibert, *et al., supra.*

[13] Itakura, K., *et al., J. Biol. Chem. 250,* 4592 (1975); Itakura, K., *et al., J. Am. Chem. Soc. 97,* 7327 (1975).

[14] It is to be understood that before a patent issued the requisite showing of novelty, utility and unobviousness required elsewhere in the patent statute would be made. The determinaton on these matters will be dependent upon the facts in each case.

produced, having enhanced survival in an environment containing penicillin.[15]

The viruses and DNA molecules themselves share the dualistic property of being chemically definable[16] compositions and propagatable by living cells. Such materials are termed "resurrectable" to signify their ability to alternate between the animate and inanimate realms.[17] Whether existing inanimate in a test tube or functioning within a living cell, the compositions remain chemically definable entities, squarely compositions of matter under § 101.

The resurrectable compositions partake of a second sort of duality, that of being simultaneously chemical compounds and information. The informational aspect is embodied in the deoxynucleotide sequence of DNA,

[15] See Hotchkiss, R. D., Jr., *Unités Biologiques Doueés de Continuité Génétique. Colloq. int. Cent. Nat. Rech. Sci., 8* 57 (1949).

[16] The viruses vary greatly in complexity. As noted *supra,* note 6, some of the simplest viruses have been completely described chemically, in terms of the nucleotide sequence of the nucleic acid component, the amino acid sequences of the protein components, and the structural and geometric relationships between the protein components and the nucleic acid. In the case of more complex viruses, the number of separate protein components comprising the protein coat and some structural features of their assembly have been determined, although the primary sequences of the nucleic acid and protein components have not been determined. The critical question is whether the chemical structure and functional properties of a virus can be described in sufficient detail to enable others of ordinary skill in the art to make and use the invention, as required by 35 U.S.C. § 112.

[17] A class of recombinant DNA cloning vectors derived from bacteriophage lambda has been designated "Charon" phages, after the mythological boatman of the river Styx. Blattner, F. R., *et al., Science 196,* 161 (1977).

which functions as information only within a living cell.[18] This Court has adverted to the informational nature of resurrectable compositions, at least by implication, in its remand of *Parker* v. *Bergy*[19] for reconsideration in the light of *Parker* v. *Flook*.[20] In view of the essentially chemical nature of cells and resurrectable compositions, and of their tangible, describable properties, the traditional legal principles relating to compositions of matter are necessarily applicable. The relevance of *Flook* to the instant case is therefore viewed as tangential. This Court has viewed askance the patentability of information *per se*[21] or processes whose essential feature is the manipulation of information.[22] However, this is not the case where the patent concerns the physical embodiment[23] of

[18] With the exception that it is technically feasible to demonstrate an aspect of the information content of DNA in a cell-free system comprising extracts of living cells and certain chemical cofactors (Zubay, G., *Ann. Rev. Genetics 7*, 267 (1973).

[19] 438 U.S. 902 (1979).

[20] 437 U.S. 584 (1978).

[21] *Leroy* v. *Latham,* 55 U.S. 156 (1852); *O'Reilly* v. *Morse,* 56 U.S. 62 (1854); *Gottschalk* v. *Benson,* 409 U.S. 63 (1972).

[22] *Parker* v. *Flook,* supra, note 20.

[23] The concept of information, as a property of matter organized in non-random fashion, as quantifiable into "bits," and as transmitted and received according to certain principles, was developed in large part in the pioneerng work of C. E. Shannon, *Bell System Tech. J. 27,* 379, 623 (1948), *reprinted in* Shannon, C. E. and Weaver, W., *The Mathematical Theory of Communication,* University of Illinois Press, Urbana, Ill. (1949). *See also* Elias, P., "Coding and Information Theory," *Reviews of Modern Physics* (1959), *reprinted in Biophysical Science—A Study* Program (J. L. Oncley, *et al,* Eds.) John Wiley and Sons, New York (1959) pp. 221-226.

information,[24] or processes manipulating an embodiment of information.[25] *Flook* did not hold that an otherwise patentable invention would be rendered unpatentable merely because the process or product had an informational aspect. The instant case provides perhaps the most clearly defined opportunity for this Court to distinguish between information *per se* and its embodiment.

The embodiment is a describable chemical compound. It can be manipulated, altered and recombined in novel and unobvious structures. As such, it falls within the category of patentable subject matter under 35 U.S.C. § 101. The fact that it simultaneously bears information is not relevant to its patentability as a product just as that same fact would not negate the patentability of a photographic emulsion or a camshaft. Furthermore, the nature of the information embodied in the deoxynucleotide sequence of DNA is not fully understood. It is a hope of science that a

[24] Information may be embodied in a photographic plate, a blueprint, a camshaft, modulated electromagnetic radiation and certain chemical compounds, to give a few simple examples. A second entity (the receiver) is necessary in order to make "sense" of any information. Patented articles involving such physical embodiments are the classic stuff of patents generally.

[25] *Cochrane* v. *Deener,* 94 U.S. 780 (1877); *Dolbear* v. *American Bell Telephone Co.,* 126 U.S. 1 (1888); *MacKay Radio & Telegraph Co.* v. *Radio Corp. of America,* 306 U.S. 86 (1939). The cases cited herein and *supra,* notes 20 and 21, were not decided in specific terms of information or its embodiment, but instead speak of mental steps, mere principles, fundamental laws of nature, algorithms and the like. Viewing these cases in terms of a distinction between information and its embodiment provides a unifying thread running throughout them all, consistent with the general rationale of *Flook.*

fuller understanding of how living cells handle genetic information will be attained.[26]

The foregoing analysis demonstrates the rationale for patentability of resurrectable compositions that can exist as inanimate chemical compounds, and suggests a boundary condition for such patentability. Substances which are unequivocally living, such as the Chakrabarty organism, are much more complex chemically. They depend for the attributes of life on the proper organized state of their chemical components.[27] Furthermore, the living cell exists in a dynamic state in which its detailed chemical composition varies with time and environmental conditions, and probably to some extent, from cell to cell. The living cell lacks the static, uniform aspect which characterizes resurrectable compositions.

Nevertheless, living cells are identifiable and describable entities which can be readily distinguished from one another by a combination of chemical, functional and morphological criteria whose development has reached a highly sophisticated plane in the field of microbiology. As a practical matter, given sufficient

[26] Following the rationale of *Flook*, it would not be possible to obtain a patent on the manner with which living cells handle specific genetic information.

[27] A living cell is "killed" by disrupting its structure, even though many of the component processes, such as metabolism, can still take place.

The fermentation process (oxidation of sugar to produce ethanol) was considered by 19th century vitalists to be dependent on living cells. It was a disappointment to Pasteur that he was unable to demonstrate cell-free fermentation. However, Eduard Buchner succeeded in 1897 where Pasteur had failed. The secret of Buchner's success lay simply in using a yeast strain in which the cells were more easily broken open.

disclosure of such properties, it would be well within the scope of ordinary skill to distinguish the Chakrabarty organism from similar organisms.

The salient feature of living compositions is their ability to reproduce themselves. Bacteria reproduce with high fidelity and may be stored for long periods of time. These properties are recognized in the current practice of placing the organism on deposit in a public type culture collection.[28] The deposit provides an adequate description of the organism even for processes in which the microorganism is arguably the sole element of novelty.

The reproduction of living cells is inherently accompanied by variation in the form of spontaneous mutation and partial genetic exchanges. For bacteria the overall probability of such events is about one in a million per generation.[29] As a culture is reproduced over several generations, it is necessary to reisolate the correct organism from a background count of variants which accumulates with each successive generation. In order to accurately identify the desired organism, one must know the criteria by which it was originally selected and these criteria must reasonably insure successful identification. Such criteria will include, for example, the selection process used to isolate the organism initially, its distinguishing functional properties and as many chemical, morphological and functional criteria as are needed to establish identity

[28] *In re Argoudelis*, 434 F.2d 1390, (C.C.P.A. 1970).

[29] By contrast higher organisms, reproducing by sexual mating, have a probability of variation of nearly 1 (diminished only by the occasional occurrence of identical twins). Certain mammalian cell lines have intermediate levels of variability, on the order of one in a thousand per generation.

according to relevant standards in the art. Therefore, it can be seen that a critical limitation on patenting compositions characterized as "living," is already present in 35 U.S.C. § 112, first paragraph, which requires a description of the invention ". . . in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same. . . ." In terms relevant to this art, compliance with § 112 should include disclosure regarding the organism's function (how to use) as well as its genetic background and selection procedure (how to make), in addition to a deposit of the organism itself.

It follows that holding the instant microorganism to be patentable subject matter will not open the floodgates for the patenting of all sorts of living organisms. The existing statutory framework coupled with the inherent properties of living organisms provides sufficiently cognizable limits, and administrative flexibility, to ensure that the law of patents remains confined to the useful arts, where it has served its function well for nearly 200 years.

III. SUMMARY

In summary, the Government's assertion [30] that "the decision to extend the patent laws from the non-living to the living is a policy judgment for Congress to make" is simplistic and misleading. The decision to hold Chakrabarty's organism patentable subject matter or not is a legal question which can and should be decided within the framework of existing statutory and case law. A rational basis can be found to provide

[30] Petitioner's Brief, footnote 44.

metes and bounds for a holding on either side of the question.

The field of biotechnology is an emerging useful art with great promise for future benefit to mankind. The constitutional purpose to promote the progress of the useful arts should be applied to promote the progress of biotechnology by providing patent protection. The boundary conditions for patenting living organisms are adequately provided in the existing patent statute, specifically 35 U.S.C. § 112, as discussed herein. Therefore, *Amicus* recommends that the decision of the Court of Customs and Patent Appeals be affirmed but that in any case, the Court's holding provide rational metes and bounds to guide the patenting of subsequent developments in this emerging technology.

Respectfully submitted,

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APPENDIX

APPENDIX A

1. Crick, F. H. C., Brenner, S., Klug, A., and Pieczenik, G., "A Speculation on the Origin of Protein Synthesis," *Origin of Life, 7,* (1976), pp. 389-397.

2. Pieczenik, G., "Theory of Genotypic Selection," Committee on Science and Technology, U.S. House of Representatives, 95th Congress, No. 24, pp. 323-340, (1977).

3. Nussinov, R., Pieczenik, G., Griggs, J., and Kleitman, D., "Algorithms for Loop Matchings," *S.I.A.M., J. Appl. Math., 35,* 1, (1978), pp. 68-82.

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7. Pieczenik, G., (1973), "The Genetic Code Constraints on Amino Acid and Nucleotide Sequences," Ph.D. Dissertation (Xerox University Microfilms, Ann Arbor, Michigan, Order No. 79-19,955), 272 pgs.

8. Pieczenik, G.

   "Multimers of Tyrosine tRNA," *J. Mol. Biol.,* (1980), *in press.*

9. Pieczenik, G.

   "Predicting Coding Function from Nucleotide Sequences or the Survival of 'Fitness' of tRNA," *Proc. Nat. Acad. Sci. USA,* (1980) *in press.*